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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	Emilio Barbera-Guillem	Examiner	:	Blanchard, David J.
Application No.	:	09/835,759	Group Art	:	1642
Filing Date	:	April 16, 2001	Docket No.	:	26983-98
Confirmation No.	:	5302			
Title	:	**VACCINE AND IMMUNOTHERAPY FOR SOLID NONLYMPHOID TUMOR AND RELATED DYSREGULATION**			

CERTIFICATE OF MAILING

Date of Deposit: **December 21, 2005**

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(Signature) December 21, 2005
(Date)

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AMENDED APPEAL BRIEF

Sir/Madam:

The following Amended Appeal Brief is submitted pursuant to the Notification of Non-Compliant Appeal Brief mailed September 21, 2005 in the above-identified application. The Notification of Non-Compliant Appeal Brief set a period of one month for reply with extensions available under 37 C.F.R. 1.136. This Amended Appeal Brief mailed with a proper certificate of mailing on December 21, 2005 with a petition for a two month extension is thus timely filed. While no additional fees are believed due, the Commissioner is hereby authorized to charge any additional fees, or credit any overpayment to Deposit Account No. 02-2051, referencing Attorney Docket No. 26983-98.

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TABLE OF AUTHORITIES

Cases

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I. REAL PARTY IN INTEREST

BioCrystal, Ltd., 575 McCorkle Boulevard, Westerville, Ohio 43082, is the assignee of the present application and the real party in interest.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

III. STATUS OF CLAIMS

Claims 1-5, 7-12, 69-73, 77, 78, 80-86, 90, 92-96, 100, 102-108, 112, 114 and 115 are pending and are on appeal (see Section IX of this document, Claims Appendix).

Claims 1, 2 and 7-10 stand rejected under 35 U.S.C. § 102(b).

Claims 1-5, 7-12, 69-73, 77, 78, 80-86, 90, 92-96, 100, 102-108, 112, 114 and 115 stand rejected under 35 U.S.C. § 103(a).

Claims 70, 71, 73, 78, 82-84, 86, 89, 90, 93, 94, 96, 100, 105, 106, 108 and 112 stand rejected under 35 U.S.C. § 112, first paragraph.

Claims 6, 13-68, 74-76, 79, 87-89, 91, 97-99, 101, 109-111, and 113 are canceled.

IV. STATUS OF AMENDMENTS

An Amendment After Appeal under 37 C.F.R. 1.116(b) filed on August 30, 2005 has been entered by the Advisory Action mailed September 13, 2005.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The pending claims are drawn to compositions that include two components. The first component is an immunotherapeutic composition for effecting B cell depletion (claims 1 and 9), one such composition being a monoclonal antibody having binding specificity for CD22 (claims 69, 82, 92 and 104). The second component is a tumor-associated antigen capable of inducing a cell mediated immune response (claims 1, 9, 69, 82, 92 and 104). Additional dependent claims add the following to the composition: anti-B cell agent (claims 4, 11, 78, 90 and 100), additional antibodies (claims 5 and 12), and immunomodulator and/or pharmaceutically acceptable carrier (claims 2, 10, 70, 72, 73, 83-86, 93-96 and 105-108). Claims 3 and 77 specify that the

composition is contained in a solid phase implant. The claimed compositions are useful for producing cellular immune responses specific for tumors.

It should be noted that, early in prosecution of this application, Appellant was subjected to a restriction requirement and was also required to elect a species of the immunotherapeutic composition for effecting B cell depletion (see Office Action mailed November 11, 2003). In a response entered February 5, 2004, Appellant elected to prosecute claims drawn to the composition described above, and also elected a species of the immunotherapeutic composition comprising a monoclonal antibody specific for CD22 (also called LL2). Therefore, as stated by the Office, most recently in the final Office Action mailed January 26, 2005 (page 2), "the claims are being examined to the extent that the affinity ligand is a monoclonal antibody specific for CD22 (LL2)..." CD22 is an antigen on the surface of B cells. This is important for examination of claims 1 and 9, since these claims do not explicitly recite a monoclonal antibody specific for CD22.

The conceptual basis for the claimed composition is that cell mediated immunity, as opposed to humoral, or antibody mediated immunity, is particularly important for anti-tumor activity in the body. An overactive humoral, or protumor, immune response may actually promote tumor progression (see specification page 7, lines 9-12). It is known that the prevalence of a particular type of CD4+ T cell is one factor influencing the type of immune response, cellular or humoral, that develops in response to an antigen. CD4+ T cells of a type called "TH1" secrete a panel of cytokines that generally support cell mediated immunity through interactions with other cells. CD4+ T cells of a type called "TH2" secrete a panel of cytokines that generally support a humoral immune response through interactions with other cells. Both TH1 and TH2 cells arise from TH0 cells. Therefore, a stimulus that pushes the immune system toward cell mediated immunity may be said to promote a TH1 response. A stimulus that pushes the immune system toward humoral, or antibody mediated immunity may be said to promote a TH2 response. The claimed composition generally influences the immune system toward cell mediated immunity promoting a TH1 response by: i) using the immunotherapeutic composition depleting B cells (B cells produce antibodies; antibodies mediate humoral immunity), and ii) the tumor-associated antigen inducing a cell mediated immune response.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. The rejection of Claims 1 (independent), 2, 7 and 8 (depend from claim 1), 9 (independent) and 10 (depend from claim 9) under 35 U.S.C. § 102(b) using Noguchi et al. (Proc. Natl. Acad. Sci. USA 92:2219-2223, 1995; "Noguchi") as evidenced by Trinchieri (Immunology Today 14:335-338, 1993; "Trinchieri").

2. The rejection of Claims 1 (independent), 2-5, 7 and 8 (depend from claim 1), 9 (independent), 10-12 (depend from claim 9), 69-73, 77, 78, 80-86, 90, 92-96, 100, 102-108, 112, 114 and 115 under 35 U.S.C. § 103(a) using Apostolopoulos et al. (Vaccine 14:930-938, 1996; "Apostolopoulos") in view of Tachibana et al. (Tokai J. Exp. Clin. Med. 8:455-463, 1983; "Tachibana"), Trinchieri, Parkhouse et al. (Current Topics in Microbiology and Immunology 182:331-335, 1992) and Wang (U.S. Pat. No. 5,939,380).

3. The rejection of Claims 70, 71, 73, 78, 82-84, 86, 89, 90, 93, 94, 96, 100, 105, 106, 108 and 112 under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement.

VII. ARGUMENT

A. Claims 1, 2 and 7-10 Are Patentable Over Noguchi As Evidenced By Trinchieri

Claims 1, 2 and 7-10 are not anticipated by Noguchi as evidenced by Trinchieri under 35 U.S.C. § 102(b).

1. Brief Discussion of Noguchi and Trinchieri References

The study described in Noguchi discloses a composition that includes interleukin-12 (IL-12) and a nonamer p53 peptide (peptide of 9 amino acids in length) in QS-21 adjuvant.

Trinchieri is a review article disclosing that IL-12 is one of a number of substances that promote TH0 cells to become TH1 cells, and inhibit TH0 cells from becoming TH2 cells.

2. Argument

In order to properly reject claims under 35 U.S.C. § 102(b), the Office must provide a reference that teaches each and every element of the claims Here, Appellant's

independent claims 1 and 9 call for, among others, an immunotherapeutic composition for effecting B cell depletion. Based on Appellant's species election, as described earlier, this immunotherapeutic composition is being examined to the extent that the immunotherapeutic composition is a monoclonal antibody specific for CD22. The applied primary reference, Nogouchi, fails to anticipate the claims.

The Office's rejection is founded on the dubious assertion that IL-12 disclosed in Noguchi, is a B cell depleting agent. It is noteworthy that Nogouchi, does not even discuss B cells or B cell depletion. Given this glaring deficiency, the Office relies on Trinchieri for the proposition that IL-12 is equivalent to a B cell depleting agent. This is incorrect.

First, Appellant notes that, like the principal reference Nogouchi, the referenced figure in Trinchieri also does not show IL-12 acting on B cells. In fact, B cells are not even shown in Figure 1.

Second, nothing in the record explicitly or inherently states the claim element – that is, a B cell depleting composition. Indeed, a close study of Trinchieri reveals that it indeed teaches away from the proposition that IL-12 and B cell depletion are equivalent. Trinchieri indicates that IL-4 is a major cytokine produced during a TH2, or humoral response (see Figure 2 of Trinchieri). Trinchieri states (page 337, column 1, lines 35-37) that the "effect of IL-4 is, however, dominant over that of IL-12." Since IL-4 would be present during a TH2 immune response (when B cells are present), its dominance over IL-12 would preclude any IL-12 activity of the type that would effect B cell depletion. This is supported by the further disclosure in Trinchieri that "once a TH1 or TH2 type of response is determined early during the immune response, it remains stable, unless major changes take place in the balance of cytokine production during the response" (Trinchieri, page 337, column 2, lines 42-48). Therefore, Trinchieri indicates that IL-12 is not an effector of B cell depletion.

The Office characterizes this as being directed to the intended use of a claimed product, thus carrying no patentable weight. Appellant believes the Office has missed the point here. The point is that IL-12 is not an effector of B cell depletion. Appellant's claims recite an immunotherapeutic composition for effecting B cell depletion. An immunotherapeutic composition that does not effect B cell depletion (i.e., IL-12) does not anticipate Appellant's claims. Appellant's argument has nothing to do with intended use of the claimed composition.

Third, Applicant's own specification teaches away from the proposition that IL-12 can be considered as an effector of B cell depletion. As seen in the experimental evidence in the specification as filed (e.g., see specification page 40, lines 4-13, and Figure 4), mice with tumors were treated with either (1) anti-mouse IgM alone, or (2) anti-mouse IgM plus IL-12. The data in Figure 4 show that the treatment with IgM plus IL-12 (Figure 4, line 3) was significantly less effective in preventing recurrence of tumors than the treatment with IgM alone (Figure 4, line 2). If IL-12 was an effector of B cell depletion, it would be expected that animals treated with IgM plus IL-12 would have less tumor recurrence than animals treated with IgM alone. This is true because, as described above, an overactive humoral, or protumor immune response promotes tumor progression. Depletion of B cells that contribute to the humoral response, therefore, would have decreased tumor recurrence in this study.

The Office has characterized this data directed toward enablement of the claimed composition. The Office also stated "that Figure 4 and the relevant text at page 40 does not indicate what immunomodulator was actually used and there are many such immunomodulators disclosed at pages 11-12 of the specification."

Appellant is bewildered by these comments. First, Appellant's argument does not bear on enablement. Rather, Appellant's argument is based on a study described in the specification suggesting that IL-12 is not an effector of B cell depletion. Again, since Appellant's claims recite an immunotherapeutic composition for effecting B cell depletion, if IL-12 does not effect B cell depletion, Noguchi does not anticipate Appellant's claims. Second, in the paragraph beginning at the top of page 40, the specification clearly states that the "immunomodulator" is IL-12. The study, whose results are shown in Figure 4 of the specification, is exactly as has been described. There is no mystery.

Therefore, lacking disclosure of a composition comprising an immunotherapeutic composition for effecting B cell depletion and a tumor-associated antigen capable of inducing a cell mediated immune response, Noguchi, even as evidenced by Trinchieri, does not anticipate Appellant's claims 1 and 9. Claims 2, 7 and 8 depend from claim 1 and claim10 depends from claim 9. Claims 2, 7, 8 and 10, therefore, are also not anticipated by Noguchi as evidenced by Trinchieri.

B. Claims 1-5, 7-12, 69-73, 77, 78, 80-86, 90, 92-96, 100, 102-108, 112, 114 And 115 Are Patentable Over Apostolopoulos In View Of Tachibana, Trinchieri, Parkhouse And Wang

Claims 1-5, 7-12, 69-73, 77, 78, 80-86, 90, 92-96, 100, 102-108, 112, 114 and 115 are not obvious in view of the combination of Apostolopoulos, Tachibana, Trinchieri, Parkhouse and Wang under 35 U.S.C. § 103(a).

1. Brief Discussion of the Apostolopoulos, Tachibana, Trinchieri, Parkhouse and Wang References

The study described in Apostolopoulos discloses that administration of a tumor-associated antigen conjugated to a carbohydrate polymer (mannan) produced a cell mediated immune response that is effective against tumors, in contrast to previous reports where administration of this tumor-associated antigen, conjugated to carriers, produced a humoral immune response and ineffective antitumor activity.

The study described in Tachibana discloses that induction of a tumor-specific humoral immune response in tumor-bearing mice, by administration of tumor-associated antigens in the context of tumor cell lines, caused enhancement of tumor growth. The study also showed that, when induction of humoral immunity was inhibited, through the use of the drug cyclophosphamide, that the enhanced tumor growth was not present.

The disclosure of Trinchieri was described earlier.

The study described in Parkhouse discloses that an anti-CD22 antibody, conjugated to ricin, depletes B cells.

The study described in Wang discloses solid phase implants for delivery of biological macromolecules.

2. Argument

Appellant's pending independent claims 1 and 9 recite a composition comprising an immunotherapeutic composition for effecting B cell depletion and a tumor-associated antigen. As stated by the Patent Office, these claims are being examined to the extent that the immunotherapeutic composition for effecting B cell depletion is a monoclonal antibody specific for CD22. Independent claims 69, 82, 92 and 104 recite a composition comprising a

monoclonal antibody specific for CD22 for effecting B cell depletion and a tumor-associated antigen capable of inducing a cell mediated immune response.

Since no single reference discloses all the elements of the above claims, the Patent Office has rejected the claims as being obvious over a combination of art (i.e., Apostolopoulos, Tachibana, Trinchieri, Parkhouse and Wang) under 35 U.S.C. § 103(a). Under 35 U.S.C. §103(a), a *prima facie* case of obvious is established if: 1) the prior art reference (or references if combined) discloses or suggests all the claim limitations (MPEP § 2143.03); 2) there is some suggestion or motivation to modify the reference to supply the missing teaching (or to combine separate references) (*In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed Cir. 1988)), and; 3) there is a reasonable expectation of success when the reference is modified (or combined) (*Yamanouchi Pharm Co. v. Danbury Phamacal, Inc.*, 231 F.3d 1339, 1343, 56 USPQ2d 1641, 1644 (Fed Cir. 2000)). Respectfully, Appellant submits that the Examiner failed to establish a *prima facie* case of obviousness regarding this rejection, based on a lack of motivation to combine the references.

With regard to motivation to combine the references, Appellant notes that it is not enough that one may modify a reference in view of a second reference, but rather it is required that one reference suggests the modification of the second reference. The Patent Office cannot use Appellant's claims as a roadmap for choosing distinct elements from the prior art without also showing motivation to combine separate references. The Court of Appeals for the Federal Circuit has restated numerous times the requirement of a teaching or suggestion to combine elements in the prior art:

> When it is necessary to select elements of various teachings in order to form the claimed invention, we ascertain whether there is any suggestion or motivation in the prior art to make the selection made by the applicant. ... "'Obviousness can not be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion, or incentive supporting the combination.'" ...
>
> ... It is impermissible ... simply to engage in hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps. ... **The references themselves must provide some teaching whereby the applicant's combination would have been obvious.**

(*In re Gorman*, 933 F.2d 982, 987, 18 U.S.P.Q.2d 1885, 1888 (Fed. Cir. 1991) (citations omitted) (emphasis added)).

Appellant notes that, of the Apostolopoulos, Tachibana, Trinchieri, Parkhouse and Wang references, the only reference that discloses an immunotherapeutic composition for effecting B cell depletion is Parkhouse, where an anti-CD22 antibody that is conjugated to the cellular toxin, ricin, is disclosed. There is simply no motivation within Parkhouse, or in the other references, to make the combination proposed by the Patent Office. Appellant's claims recite an anti-CD22 antibody to effect B cell depletion, while Parkhouse discloses an anti-CD22 antibody conjugated to the cellular toxin, ricin. Given the anti-CD22 antibody-ricin conjugate of Parkhouse, at best, it might have been obvious to try anti-CD22 antibody alone to see if B cells could be depleted. However, "obvious to try" is not sufficient to provide a motivation to combine references under 35 U.S.C. § 103(a) (*In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)). Therefore, Appellant does not believe that there is motivation within Parkhouse to combine this reference with a reference disclosing a tumor-associated antigen, as would be required to render the pending claims obvious. Additionally, Appellant does not believe there is motivation to combine with Parkhouse in the other references cited by the Patent Office. None of those references (Apostolopoulos, Tachibana, Trinchieri and Wang) teach or suggest specifically depleting B cells and certainly do not teach or suggest depleting B cells with an anti-CD22 antibody.

Additionally, there must be a reasonable expectation that combining of references or modifying a reference would produce a successful result (*Yamanouchi Pharm Co. v. Danbury Phamacal, Inc.*, 231 F.3d 1339, 1343, 56 USPQ2d 1641, 1644 (Fed Cir. 2000)). Appellant's claims recite an anti-CD22 antibody to effect B cell depletion. However, Parkhouse discloses an anti-CD22 antibody conjugated to ricin. In order for Parkhouse to supply the teaching of depleting B cells, there would have to be a reasonable expectation that modifying the anti-CD22-ricin conjugate to anti-CD22 without the conjugated ricin would be able to effect B cell depletion. Given the high toxicity of ricin (see Lord, J. M., et al. 1994. Ricin: structure, mode of action, and some current applications. FASEB J. 8:201-208; a copy of this reference is in the Evidence Appendix beginning on page 25 of this document), there is not a reasonable expectation that anti-CD22 antibody alone, without ricin, would be successful in effecting B cell depletion. Therefore, Appellant does not believe that there is a reasonable expectation that

modification of the disclosure in Parkhouse, to anti-CD22 antibody alone, would provide the required reasonable expectation of success.

In the final Office Action mailed January 26, 2005, the Patent Office stated (pages 9 and 10) that the motivation to combine the cited references comes from Apostolopoulos. Apostolopoulos discloses administration of a particular, mannan-conjugated tumor-associated antigen to produce a cell mediated immune response that is effective against tumors, where previous tumor-associated antigens, conjugated to carriers, produced a humoral immune response and inefficient antitumor activity. Although Apostolopoulos discloses tumor-specific antigens, Apostolopoulos does not disclose or suggest depleting B cells. Apostolopoulos merely discloses that conjugation of tumor-specific antigens with certain carriers may facilitate a tumor-specific antigen in producing a cell mediated immune response rather than a humoral immune response. There is no teaching or suggestion within Apostolopoulos that humoral immunity could or should be suppressed. There is no motivation to attempt to deplete B cells. There is no motivation to use an anti-CD22 antibody to deplete B cells.

The Patent Office also stated in the final Office Action (page 9) that motivation to combine the references also comes from Tachibana, which states "immune complexes interfere with cell-mediated immunity to cause enhancement of tumor growth" and "the enhancement of tumor growth was caused by acceleration of humoral response existing beforehand in the tumor-bearing state." Disclosing that humoral immune responses inhibit cell mediated antitumor activity is not the same as disclosing or suggesting depletion of B cells or depletion of B cells with anti-CD22 antibody to eliminate a humoral immune response. Again, the only reference cited by the Patent Office that discloses an immunotherapeutic composition for effecting B cell depletion is Parkhouse. One would not be motivated to combine Tachibana with Parkhouse to come up with a composition containing an anti-CD22 antibody that alone is sufficient to deplete B cells. The anti-CD22 antibody disclosed in Parkhouse is conjugated to ricin. While it might be "obvious to try" anti-CD22 antibody without ricin to deplete B cells based on Parkhouse, that something is obvious to try is not sufficient motivation to combine or modify a reference (*In re O'Farrell*).

C. Claims 70, 71, 73, 78, 82-84, 86, 89, 90, 93, 94, 96, 100, 105, 106, 108 And 112 Meet The Written Description Requirement

Claims 70, 71, 73, 78, 82-84, 86, 89, 90, 93, 94, 96, 100, 105, 106, 108 and 112 meet the written description requirement 35 U.S.C. § 112, first paragraph.

1. Argument

In the final Office Action mailed January 26, 2005, the Patent Office stated (pages 11-14) that certain claim elements were not described in the specification in a manner that reasonable conveys to one skilled in the art that the inventor was in full possession of the invention at the time the application was filed. More specifically, the Patent Office referenced the Written Description Guidelines for examination of patent applications (page 12) which states:

> the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus.

(Federal Register 66:1099-1111; MPEP § 2164 (emphasis added)).

In particular, the Patent Office stated (final Office Action, page 12) that the words "immunomodulator" (claims 2, 10, 70, 72, 73, 83-86, 93-96 and 105-108) as used in the phrase "immunomodulator for inducing a cell mediated immune response comprising a Th1" and the phrase "anti-B cell agent" (claims 4, 11, 78, 90 and 100) as used in the phrase "an anti-B cell agent for effecting B cell depletion" do not meet the written description requirement. The Patent Office asserts that there is not sufficient description in the specification of these terms (e.g., relevant identifying characteristics, such as physical and/or chemical properties and structure) to demonstrate full possession of the invention at the time the application was filed.

This assessment is incorrect. Appellant below, cites portions of the specification as filed with respect to both "immunomodulator" and "anti-B cell agent." Based on these passages from the specification, it is clear that these descriptions meet the written description requirements, as set forth in the passage from the Written Description Guidelines, cited above.

As to the term "immunomodulator," attention is directed to the paragraph beginning on page 11 of the application. This paragraph is reproduced in its entirety below, with underlined portions directed to representative species of immunomodulators:

> The term "immunomodulator" is used herein, for purposes of the specification and claims, to mean one or more compositions that, when administered to an individual in an effective amount, induces a cell mediated immune response comprising a TH1 response, and more preferably, may also induce a cytotoxic CD8+ T cell response. As known to those skilled in the art, a composition that may induce a cell mediated immune response comprising a TH1 response may include, but is not limited to, IL-12, IL-12 and melatonin, flavone acetic acid (flavonoid, 2-heteroaryl flavonoid derivatives, flavone-8-acetic acid), QS-21(a purified form of saponin, at a high dose) and monophosphoryl lipid A, N-acetylcysteine, SAF-1 (Syntex adjuvant formulation-1), AS101 (ammonium trichloro (dioxoethylene-O,O') tellurate), lentinan (a fungal branched 1.fwdarw.3-(beta)-D-glycan), TraT protein ("ISCAR" or immunostimulatory carrier- an integral membrane protein of E. coli), Viscum album extract (commercially available extract of mistletoe), Z-100 (a lipid arabinomannan-containing extract of M. tuberculosis), OK-432 (Picibanil, inactivated and heat treated S. pyogenes Su strain), immunostimulatory DNA sequences, and the like. For example, IL-12 has been shown to be a potent inducer of naive CD4+ cells towards a cell mediated immune response comprising a TH1 response. IL-12 may be administered to a human individual as a cytokine in solution (e.g., rIL-12 in a dose ranging from about 10 ng/kg to about 300 ng/kg, twice weekly, subcutaneously or intratumoral), or in the form of dendritic cells or fibroblasts genetically engineered to express human IL-12 (see, e.g., Lotze et al., 1997, Cancer J. Sci. Am. 3/S (S109-S114), herein incorporated by reference). In another example, short bacterial immunostimulatory DNA sequences containing unmethylated CpG motifs have been shown to be able to stimulate a TH1 response (e.g., by inducing IL-12 production), and hence stimulate a cell-mediated immune response (Roman et al., 1997, Nat. Med. 3:849-854; Lipford et al., 1997, Eur. J. Immunol. 27: 3420-3426, herein incorporated by reference). An amount of an immunomodulator effective to induce a cell mediated immune response comprising a TH1 response will vary depending on such factors as the mode of administration, individual's age, weight, general medical condition, and immune status. For purposes of illustration, but not limitation, lentinan has been administered intravenously (e.g., 2 mg, 3 times per week), melatonin has been administered orally (e.g., 20 mg/day in the evening), Viscum album has been administered subcutaneously (e.g., 2-3 times per week, ranging from 0.1 to 30 mg), AS101 has been administered by intravenous drip (e.g., in a range of from about 3 mg/m.sup.2 to about 12 mg/m.sup.2), and QS-21 has been administered subcutaneously (e.g., in a range of from about 100 .mu.g to about 200 μg). A preferred immunomodulator may be used in the present invention to the exclusion of an immunomodulator other than the preferred immunomodulator.

This paragraph provides more than sufficient description of the term "immunomodulator" to meet the written description requirement. At the very least, the paragraph provides sufficient description of a representative number of species of immunomodulators to demonstrate full possession of the invention.

As to the term "anti-B cell agent," attention is directed to the paragraph beginning at the bottom of page 8 of the application. Portions of this paragraph are reproduced below, with underlined portions directed to representative species of immunomodulators:

> In another embodiment the affinity ligand, which comprises the immunotherapeutic composition, may further comprise at least one anti-B cell agent. The "anti-B cell agent" comprises a cytolytic agent (e.g., the agent itself or a vector that is introduced into B cells and therein the vector encodes a cytolytic agent). The anti-B cell agent may be coupled to the affinity ligand using methods known in the art for coupling affinity ligands to other molecules (See, for example, conjugates as reviewed by Ghetie et al., 1994, Pharmacol. Ther. 63:209-34; U.S. Pat. No. 5,789,554, the disclosure of which is herein incorporated by reference). Often such methods utilize one of several available heterobifunctional reagents used for coupling or linking molecules. The affinity ligand serves to selectively bind the B cells, thereby bringing the anti-B cell agent in contact with or in functional proximity of B cells. A cytolytic agent is an agent that, by interacting directly with such B cells, causes B cell cytotoxicity. Such cytolytic agents may include, but are not limited to, a therapeutically effective amount of toxins; drugs; enzymes; cytokines; radionuclides; photodynamic agents; and molecules which induce apoptosis (e.g., Fas ligand; a Fas ligand expressing vector has been described in more detail in by the present inventor in Gene Therapy 8:209-214, 2001, the disclosure of which is herein incorporated by reference). Toxins may include a cytolytically effective amount of ricin A chain, mutant Pseudomonas exotoxins, diphtheria toxoid, streptonigrin, boamycin, saporin, gelonin, pokeweed antiviral protein, or the like. Drugs may include an effective amount of cytotoxic drug including, but not limited to, fludarabine, chlorambucil, daunorubicin, doxorubicin (e.g., in liposomes), cisplatin, bleomycin, melphalan, mitomycin-C, and methotrexate. A preferred cytotoxic drug may be used as an anti-B cell agent in the present invention to the exclusion of a cytotoxic drug other than the preferred cytotoxic drug. Due to the sensitivity of B cells to radiation, a radionuclide may include, but is not limited to, a radiometal such as yttrium which emits a high energy beta particle, and I^{125} that emits Auger electrons, that may be absorbed by adjacent B cells. A photodynamic agent may include a cytolytically effective amount of a porphyrin or a porphryin derivative as known in the art. A preferred anti-B cell agent may be used in the present invention to the exclusion of an anti-B cell agent other than the preferred anti-B cell agent.

This passage provides more than sufficient description of the term "anti-B cell agent" to meet the written description requirement. At the very least, the paragraph

provides sufficient description of a representative number of species of anti-B cell agents to demonstrate full possession of the invention.

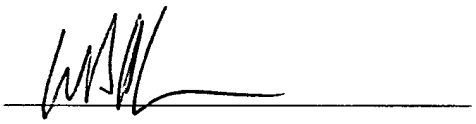
D. Conclusion

Appellant believes that the remarks presented above resolve all outstanding issues concerning the above-referenced application. Accordingly, Appellant as the appealed claims are allowable, the final rejection should be reversed and the case remanded to the Examiner with instruction to pass the application to allowance.

While no fees are believed due, the Commissioner is hereby authorized to charge any additional fees, or credit any overpayment to Deposit Account No. 02-2051, referencing Attorney Docket No. 26983-98.

Respectfully submitted,

Dated: 21 DEC 2005

By: 

W. Scott Harders
Registration No. 42,629

BENESCH, FRIEDLANDER, COPLAN & ARONOFF, LLP
2300 BP Tower
200 Public Square
Cleveland, OH 44114
Direct Dial: (216) 363-4500

VIII. CLAIMS APPENDIX

1. (previously presented) A composition for treating a TH2 response and for inducing a cell mediated immune response comprising a TH1 response in an individual having a TH2/TH1 imbalance associated with a pro-tumor immune response, the composition comprising: an immunotherapeutic composition for effecting B cell depletion; and tumor-associated antigen capable of inducing a cell mediated immune response comprising a TH1 response.

2. (previously presented) The composition according to claim 1, further comprising a component selected from the group consisting of an immunomodulator for inducing a cell mediated immune response comprising a TH1 response, a pharmaceutically acceptable carrier, and a combination thereof.

3. (previously presented) The composition according to claim 1, wherein the immunotherapeutic composition is contained in a solid phase implant for delivery of the immunotherapeutic composition.

4. (previously presented) The composition according to claim 1, wherein the immunotherapeutic composition further comprises an anti-B cell agent.

5. (previously presented) The composition according to claim 1, wherein the immunotherapeutic composition comprises an affinity ligand having binding specificity for a determinant selected from the group consisting of CD19, CD20, CD21, CD22 (also known as LL2), CDIM, and Lym-1.

6. (canceled)

7. (previously presented) The composition according to claim 1, wherein the TH2/TH1 imbalance is mediated by a disease process comprising a pro-tumor immune response.

8. (previously presented) The composition according to claim 1, wherein the TH2/TH1 imbalance is mediated by a disease process comprising a pro-tumor immune response and solid nonlymphoid tumor.

9. (previously presented) A composition useful for the treatment of solid nonlymphoid tumor in an individual, the composition comprising: an immunotherapeutic composition for effecting B cell depletion; and tumor-associated antigen capable of inducing a cell mediated immune response comprising a TH1 response;

wherein the composition is in an amount effective to overcome a TH2/TH1 imbalance, the TH2/TH1 imbalance associated with a pro-tumor immune response, or a combination of the solid nonlymphoid tumor and a pro-tumor immune response.

10. (previously presented) The composition according to claim 9, further comprising a component selected from the group consisting of an immunomodulator for inducing a cell mediated immune response comprising a TH1 response, a pharmaceutically acceptable carrier, and a combination thereof.

11. (previously presented) The composition according to claim 9, wherein the immunotherapeutic composition further comprises an anti-B cell agent.

12. (previously presented) The composition according to claim 9, wherein the immunotherapeutic composition comprises an affinity ligand having binding specificity for a determinant selected from the group consisting of CD19, CD20, CD21, CD22 (also known as LL2), CDIM, and Lym-1.

13-68. (canceled)

69. (previously presented) A composition comprising:

(a) an immunotherapeutic composition comprising a monoclonal antibody having binding specificity for CD22 for effecting B cell depletion; and

(b) tumor-associated antigen capable of inducing a cell mediated immune response comprising a TH1 response;

wherein the composition is in an amount effective for suppressing a TH2 response, and for inducing a cell mediated immune response comprising a TH1 response, in an individual having a TH2/TH1 imbalance associated with a pro-tumor immune response.

70. (previously presented) The composition according to claim 69, further comprising a component selected from the group consisting of an immunomodulator for inducing a cell mediated immune response comprising a TH1 response, a pharmaceutically acceptable carrier, and a combination thereof.

71. (previously presented) The composition according to claim 69, further comprising an immunomodulator for inducing a cell mediated immune response comprising a TH1 response.

72. (previously presented) The composition according to claim 69, wherein the immunotherapeutic composition further comprises a pharmaceutically acceptable carrier, and the tumor-associated antigen further comprises a pharmaceutically acceptable carrier.

73. (previously presented) The composition according to claim 70, wherein the component comprises an immunomodulator and a pharmaceutically acceptable carrier.

74-76. (canceled)

77. (previously presented) The composition according to claim 74, wherein the immunotherapeutic composition is contained in a solid phase implant for delivery of the immunotherapeutic composition.

78. (previously presented) The composition according to claim 69, wherein the immunotherapeutic composition further comprises an anti-B cell agent.

79. (canceled)

80. (previously presented) The composition according to claim 69, wherein the TH2/TH1 imbalance is mediated by a disease process comprising a pro-tumor immune response.

81. (previously presented) The composition according to claim 69, wherein the TH2/TH1 imbalance is mediated by a disease process comprising a pro-tumor immune response and solid nonlymphoid tumor.

82. (previously presented) A composition comprising:

(a) an immunotherapeutic composition comprising a monoclonal antibody having binding specificity for CD22 for effecting B cell depletion; and

(b) tumor-associated antigen capable of inducing a cell mediated immune response comprising a TH1 response;

wherein the composition is in an effective amount for the treatment, or inhibition of development, of solid nonlymphoid tumor in an individual having a pro-tumor immune response.

83. (previously presented) The composition according to claim 82, further comprising a component selected from the group consisting of an immunomodulator for inducing a cell mediated immune response comprising a TH1 response, a pharmaceutically acceptable carrier, and a combination thereof.

84. (previously presented) The composition according to claim 82, further comprising an immunomodulator for inducing a cell mediated immune response comprising a TH1 response.

85. (previously presented) The composition according to claim 82, wherein the immunotherapeutic composition further comprises a pharmaceutically acceptable carrier, and the tumor-associated antigen further comprises a pharmaceutically acceptable carrier.

86. (previously presented) The composition according to claim 83, wherein the component comprises an immunomodulator and a pharmaceutically acceptable carrier.

87-89. (canceled)

90. (previously presented) The composition according to claim 82, wherein the immunotherapeutic composition further comprises an anti-B cell agent.

91. (canceled)

92. (previously presented) A composition comprising:

(a) an immunotherapeutic composition comprising a monoclonal antibody having binding specificity for CD22, for effecting B cell depletion in suppressing a TH2 response associated with a pro-tumor immune response or a combination of a pro-tumor immune response and solid nonlymphoid tumor; and

b) tumor-associated antigen capable of inducing a cell mediated immune response comprising a TH1 response.

93. (previously presented) The composition according to claim 92, further comprising a component selected from the group consisting of an immunomodulator for inducing a cell mediated immune response comprising a TH1 response, a pharmaceutically acceptable carrier, and a combination thereof.

94. (previously presented) The composition according to claim 93, further comprising an immunomodulator for inducing a cell mediated immune response comprising a TH1 response.

95. (previously presented) The composition according to claim 92, wherein the immunotherapeutic composition further comprises a pharmaceutically acceptable carrier, and the tumor-associated antigen further comprises a pharmaceutically acceptable carrier.

96. (previously presented) The composition according to claim 93, wherein the component comprises an immunomodulator and a pharmaceutically acceptable carrier.

97-99. (canceled)

100. (previously presented) The composition according to claim 92, wherein the immunotherapeutic composition further comprises an anti-B cell agent.

101. (canceled)

102. (previously presented) The composition according to claim 92, wherein the TH2/TH1 imbalance is mediated by a disease process comprising a pro-tumor immune response.

103. (previously presented) The composition according to claim 92, wherein the TH2/TH1 imbalance is mediated by a disease process comprising a pro-tumor immune response and solid nonlymphoid tumor.

104. (previously presented) A composition comprising:

(a) an immunotherapeutic composition comprising a monoclonal antibody having binding specificity for CD22 for effecting B cell depletion in suppressing a TH2 response; and

(b) tumor-associated antigen capable of inducing a cell mediated immune response comprising a TH1 response;

wherein the composition is in an amount effective to overcome a TH2/TH1 imbalance associated with a pro-tumor immune response, or a combination of solid nonlymphoid tumor and a pro-tumor immune response.

105. (previously presented) The composition according to claim 104, further comprising a component selected from the group consisting of an immunomodulator for inducing a cell mediated immune response comprising a TH1 response, a pharmaceutically acceptable carrier, and a combination thereof.

106. (previously presented) The composition according to claim 104, further comprising an immunomodulator for inducing a cell mediated immune response comprising a TH1 response.

107. (previously presented) The composition according to claim 104, wherein the immunotherapeutic composition further comprises a pharmaceutically acceptable carrier, and the tumor-associated antigen further comprises a pharmaceutically acceptable carrier.

108. (previously presented) The composition according to claim 105, wherein the component comprises an immunomodulator and a pharmaceutically acceptable carrier.

109-111. (canceled)

112. (previously presented) The composition according to claim 104, wherein the immunotherapeutic composition further comprises an anti-B cell agent.

113. (canceled)

114. (previously presented) The composition according to claim 104, wherein the TH2/TH1 imbalance is mediated by a disease process comprising a pro-tumor immune response.

115. (previously presented) The composition according to claim 104, wherein the TH2/TH1 imbalance is mediated by a disease process comprising a pro-tumor immune response and solid nonlymphoid tumor.

IX. EVIDENCE APPENDIX

None.

X. RELATED PROCEEDINGS APPENDIX

None.